## Remarks

Claims 6-14 are pending.

With regard to the quantity of experimentation that would be required to achieve the claimed technology *in vivo*, and the delivery and penetration of triplex forming oligonucleotides into tissues of intact animals, the Applicants have provided studies demonstrating the substantial uptake in a number of tissues except for the brain (brain tissue mutagenesis measured as an internal control because of the blood brain barrier). As evident from Table 1 (Previously submitted Declaration by Dr. Peter Glazer; November 15, 2002), the average mutation frequencies in liver, kidney, skin, colon, small intestine, and lung, as a result of the triplex forming oligonucleotide binding to the polypurine site in *supFG1* (AG30), were significantly higher than tissues derived from the control treated mice. Furthermore, the Applicants have addressed, and eliminated, the notion that the induced mutagenesis obtained from the AG30 treated animals may have resulted from a non-specific effect. This is based upon a lambda cII gene mutation reporter that showed no induction of mutagenesis in animals treated with either AG30 or the negative control oligonucleotide (SCR30) as compared with background levels (see Table 2). These results are consistent with a ***gene-specific***, triplex mediated effect of AG30 in inducing mutagenesis in the *supFG1* gene of mice.

**Rejection Under 35 U.S.C. § 112, first paragraph**

Claims 6-14 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the below arguments.

The Examiner has quoted the M.P.E.P. § 2164.05(a) to support his assertion that references dated after the filing date cannot be used to show what was known of the time of filing. It should also be noted that the very same paragraph cited by the Examiner, further states, "...applicant can offer the testimony of an expert based on the publication as evidence of the level of skill in the art at the time the application was filed." *Gould v. Quigg*, 822 F2.d 1074, 1077, 3 USPQ2d 1302, 1304 Fed. Cir. 1987. Furthermore, with regard to post-filing art, the CAFC stated in In re Brana, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995), that a post-filing date declaration setting forth test results substantiating utility "pertains to the accuracy of a statement already in the specification. . . . It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed." An important distinction has been made by the Courts between evidence of the knowledge and ability of those of skill in the art at the time of filing and evidence to prove that statements made in the application are correct. In the former case, of course, only evidence which existed prior to the filing of the application, or evidence that certain knowledge existed at the time of filing, is admissible (In re Hogan, 194 USPQ 527 (CCPA 1977)). In the latter case, as in this case, any evidence, developed at any time, may be submitted for consideration.

The clearest affirmation of the seasonability of factual evidence developed after the filing date of an application is provided by the Court in In re Marzocchi (169 USPQ 367, 370 (CCPA 1971)). In discussing rejections under 35 USC 112 where an examiner asserts that the unpredictability of the art creates a reasonable doubt as to the accuracy of a particular broad statement (in the application) supporting enablement, the Court states:

> Most often, additional factors, such as the teachings of pertinent references[*], will be available to substantiate any doubts that the asserted scope of enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof.
>
> ***
>
> Not necessarily *prior* art references, it should be noted, since the question would be regarding the *accuracy* of a statement in the specification, not whether that statement had been made before. [emphasis in the original]

*Id. at 367*

In *In re Wilson* (135 USPQ 442, 444 (CCPA 1962)), the Court agreed that a reference, published after the filing date of the application, was properly cited to show a state of fact. In *In re Langer* (183 USPQ 288, 297 (CCPA 1974)), the Court again noted that later published references "are properly cited for the purpose of showing a fact." In *In re Rainer* (134 USPQ 343, 345 (CCPA 1962)) the Court found no error in the limited use made of a reference

published after Appellant's filing date to show a fact. While all of these cases involved publications cited by the Patent Office in support of rejections, the same standard applies to evidence cited by Appellant. See In re Hogan.

There is no legal requirement that an inventor have actually reduced the invention to practice prior to filing. MPEP at § 2164.02, *citing* Gould v. Quigg, 822 F.2d 1074 (Fed. Cir. 1987). "The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." *Id.*

In view of the foregoing discussion, the applicants respectfully ask the Examiner to again review the specification *in view of the Glazer Declaration* (and enclosed references herewith; cited in the Declaration). The applicants submit that the application, as filed, clearly teaches how to make and use the claimed methods. Practicing the claimed methods would not be considered undue in view of the Declaration mailed on November 15, 2002 ("Glazer Declaration"). Using the methods and reagents provided in the present specification, method embodiments are explicitly described in the Glazer Declaration and detail the administration of intraperitoneal injections of two different triplex forming oligonucleotides to mice. *Mutagenic analysis on collected tissues confirmed an oligonucleotide-specific induction of mutagenesis in these mice.* "These data indicate efficient tissue uptake and distribution of oligonucleotides in mice after i.p. injections" (see page 9 of Declaration). The Examiner asserts that the quantity of experimentation is undue, since there exists a number of parameters which would have to be

studied to apply this technology to *in vivo* methods. It should be pointed out that each of (a), the ability of the oligonucleotide to specifically bind the target gene, (b), formation of a stable complex between the oligonucleotide and the target gene, (c), uptake of the oligonucleotide by the cell, and (d), solubility of the oligonucleotide in the cell, have all been addressed in the previously submitted declaration (Glazer Declaration).

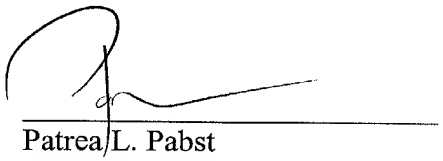
The Examiner has stated that "there exists no correlation between the entry of the oligonucleotide-mutagen complex in an isolated cells *ex vivo* method and *in vivo* applications where entry into an animal is required" (referring to *in vitro* methods of targeted mutagenesis of the *supF* gene). Again, the claimed methods are disclosed in the specification in such a manner that one skilled in the art is able to practice them without an undue amount of experimentation. The Glazer Declaration clearly illustrates this point. For example, transgenic mice bearing chromosomal copies of the *supF* and *cII* reporter genes were treated with a *supF* targeted triplex forming oligonucleotide. The results indicated a fivefold greater mutation frequency in the *supF* gene (no mutagenesis was detected in the control gene (*cII*) with either of the *supF* oligomer or scrambled sequence control oligomer).

The Examiner points to references (see page 4 of the Office Action mailed on January 16, 2003) which allegedly cast doubt on the stability of triplexes *ex vivo* (Lin *et al.*, 2000), whether purine or pyrimidine TFOs are compatible with triplex formation (Puri *et al.*, 2001), whether higher order target structures can be comprehended in order to predict the potential of an inhibitory oligo (Uhlmann *et al.*, 1990), and whether the stability of ribozymes in the presence of

proteins, intracellular enzymes, and nucleases is compromised (Mirabelli *et al.*, 1991). The assertions made by the Examiner, with regard to unpredictability in the art and allegedly supported by the foregoing four references, are rendered moot in view of the Glazer Declaration. The results presented therein rule out any *nonspecific* mutagenic effect of a triplex forming oligonucleotide and are consistent with a gene-specific, triplex-mediated effect of the oligonucleotide in inducing an increased level of mutagenesis in the *supFG1* gene of 3340 mice.

Allowance of claims 6-14 is respectfully solicited.

Respectfully submitted,



Patrea L. Pabst
Reg. No. 31,284

Date: April 16, 2003

HOLLAND & KNIGHT LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, Georgia 30309-3400
(404) 817-8473
(404) 817-8588 (Fax)

**Certificate of Mailing Under 37 C.F.R. § 1.8(a)**

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Commissioner for Patents, Washington, D.C. 20231.

Aisha Wyatt

Date: April 16, 2003